(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 May 2007 (18.05.2007)

PCT

(10) International Publication Number
WO 2007/054976 A2

(51) International Patent Classification:
A61K 9/26 (2006.01) *A61K 47/14* (2006.01)
A61K 47/44 (2006.01) *A61K 47/32* (2006.01)

(21) International Application Number:
PCT/IN2006/000438

(22) International Filing Date:
7 November 2006 (07.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2985DEL/2005 8 November 2005 (08.11.2005) IN

(71) Applicant *(for all designated States except US)*: **PANACEA BIOTEC LTD.** [IN/IN]; B-1 Extn./A-27, Mohan Co-Operative Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JAIN, Rajesh** [IN/IN]; Panacea Biotec Ltd, B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044 (IN). **JINDAL, Kour, Chand** [IN/IN]; Panacea Biotec Ltd, B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044 (IN). **DEVARAJAN, Sampath, Kumar**; Panacea Biotec Ltd. B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044 (IN).

(74) Agent: **GUPTA, Bhartee**; Panacea Biotec Ltd., B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *without international search report and to be republished upon receipt of that report*

For two letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL LIPID BASED CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Novel controlled release pharmaceutical compositions are provided which release the active agent(s) over an extended period of time comprising a core wherein the said core comprises at least one active agent(s) which is preferably water soluble, a lipid system comprising at least one lipid component(s), at least one water insoluble release modifier(s), at least one channel forming agent(s) and optionally one or more pharmaceutically acceptable excipients; and at least one coat. Preferably the coating composition comprises at least one hydrophilic pH independent polymer(s) and optionally one or more pharmaceutically acceptable excipients. Also provided is a process of preparation of such compositions and method of using them.

WO 2007/054976 A2

NOVEL LIPID BASED CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to novel controlled release pharmaceutical compositions and process of preparation of such compositions comprising a core wherein the said core comprises at least one active agent(s) or its pharmaceutically acceptable salts, derivatives, isomers, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, a lipid system comprising at least one lipid component(s), at least one water insoluble release modifier(s), at least one channel forming agent(s) and optionally one or more pharmaceutically acceptable excipients; and at least one coat; wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time. Particularly the present invention relates to compositions comprising alfuzosin or pramipexole or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. Further, this invention relates to process of preparation of such novel compositions and method of using them.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well-known in the pharmaceutical field and include the ability to release the medicament in a controlled manner over a period of time while increasing patient compliance by reducing the number of administrations necessary to achieve the same level. Several controlled release compositions for delivering different pharmaceutically active ingredients and involving different release mechanisms had been described previously.

US patent no. 4,851,232 describes a hydrogel reservoir containing tiny pills having an active agent core surrounded by a wall controlling delivery of active agent to the stomach. The hydrogel swells in the stomach to facilitate retention of the active agent reservoir in the stomach over time. US patent no. 4,871,548 describes a dosage form including a mixture of low and high number average molecular weight hydroxypropyl methylcellulose polymers and active agent that swells when in the stomach. US patent no. 6,548,083 describes a gastro-retentive controlled release dosage form comprising an active agent and a polymer matrix formed of a mixture of a swellable, water soluble polymer. US publication no. 2004185105 describes a method for selecting an optimized controlled release dosage form for administration to a patient having a predetermined drug release profile in vivo by

preparing a plurality of different candidate dosage forms each comprised of a biocompatible, hydrophilic polymer and a pharmacologically active agent incorporated therein. US patent no. 5,007,790 describes a sustained-release oral drug dosage form for releasing a solution of drug into the stomach comprising a plurality of solid particles of a solid-state drug dispersed within a hydrophilic, water-swellable polymer.

Alfuzosin acts as a selective and competitive antagonist of alpha-1 adrenoceptor mediated contraction of prostatic capsule, bladder base and proximal urethral structures and used in the treatment of moderate to severe symptoms of benign prostatic hyperplasia. Alfuzosin is reported to be absorbed preferentially in the upper part of the gastrointestinal tract and, in particular, being absorbed in the duodenum and the jejunum. Alfuzosin is conventionally administered three times per day as 2.5 mg immediate release tablet dosage form. Hence, sustained release compositions of alfuzosin provide various advantages over conventional multiple dosing including better patient compliance, reduced fluctuations of plasma drug levels, and reduced toxicity. A once daily formulation of alfuzosin (10mg), Xatral®-XL (available in Europe) and UroXatral® (available in the US), provides equivalent systemic exposure when compared to the 2.5 mg immediate release tablet dosage form of alfuzosin administered thrice daily. The alfuzosin 5 mg extended release dosage form may be given to adults twice daily, with the first dose taken at bedtime. Pramipexole is a non-ergot dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little pre-systemic metabolism. Pramipexole is extensively distributed and displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers.

Biguanides such as Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type-2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Sulfonylureas such as Glibenclamide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The combination of sulfonylurea and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms. Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator activated receptor-gamma. In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization.

US patent no. 6,149, 940 discloses a preparation of an alfuzosin 10 mg once daily composition for oral delivery using a technology termed Geomatrix that has been developed by Jagotec-AG. The three-layer Geomatrix tablet consists of a hydrophilic active matrix core containing alfuzosin hydrochloride and two inert, functional layers, one swellable layer and one erodible layer, whose functions are to control the hydration and swelling rate of the core, and thereby controlling the dissolution of the drug. When the tablet comes into contact with gastric juices, it increases considerably in volume and thus remains in the stomach for a longer time. In this manner, most of the drug is absorbed in a controlled manner in the portion of the gastrointestinal tract having the highest capacity for absorption. Alfuzosin is released in zero order from the dosage form developed using this technology. However, the manufacture of multi-layered tablets by this technology involves highly skilled personals, special facilities, is time consuming, complex to produce, and hence, relatively expensive as compared to simple matrix type single layered tablets. Hence, developing controlled release dosage form of alfuzosin as described in the present invention particularly using two functional excipients are simple and convenient process as compared to the manufacture of multi-layered tablets.

US patent no. 5,589, 190 discloses a pharmaceutical composition which comprises at least one coated core that contains alfuzosin hydrochloride, which core is coated with a coating that contains a polymer that is insoluble in acid and soluble at pH 7 or above, and at least one uncoated core containing alfuzosin hydrochloride. Thus the sustained release of a part of alfuzosin from the said composition is governed by the coating. Further, the

said patent discloses a combination of two types of tablets one coated and the other uncoated with different release rates that are filled into hard gelatin capsules. These formulations, however, have several disadvantages including the need for strict process controls during their manufacture and unpredictability in cumulative drug release profile.

The PCT publication bearing no. WO2004/037228 discloses a sustained release oral dosage form comprising a single functional layer, and optionally, one or more nonfunctional layers adjacent to the single functional layer, wherein the single functional layer comprises alfuzosin and one or more release retarding ingredients such as one or more of cellulosic polymers, methacrylate polymers, acrylic acid polymers, block copolymers, gums and polyethylene oxide. The non-functional layer does not contain drug but one non-functional layer (first layer) acts as a swelling layer and other comprises hydrophobic material (third layer) like hydrogenated castor oil, glyceryl monostearate or wax used to slow down the penetration of water and or aqueous fluids into the second layer containing the active substance and into the first and third layer. The said publication primarily describes the use of hydroxypropyl methylcellulose (HPMC) polymer as release retarding agent. This system works by initial swelling of matrix followed by erosion of gelled layers to produce the zero order release pattern of the drug. The said PCT application thus specifically teaches the use of HPMC to produce a hydrophilic core based system in the form of single matrix tablets. EP 700285 discloses drug delivery compositions of alpha adrenoceptor blocking agents that have a biphasic drug release profile. This patent teaches matrix compositions using HPMC and a coating designed to dissolve in the colonic environment.

The PCT publication bearing no. WO 200565641 discloses a non-disintegrating, non-eroding, non-bioadhesive and non-swelling oral controlled release pharmaceutical composition comprising at least one high dose water soluble active ingredient, at least one diluent, at least one binder, and a polymer system comprising of at least one release controlling polymer optionally with other pharmaceutically acceptable excipients. However, the core matrix compositions described in the said publication are particularly hydrophilic in nature due to the substantially high content of the water soluble active agent present in the core composition. Moreover the compositions disclosed are particularly uncoated compositions, and thus the rate of release of the active agent from the composition is solely controlled by the hydrophilic core matrix.

The PCT publication bearing no. WO 200469228 relates to a sustained release tablet formulation comprising venlafaxine, a sustained release agent selected from povidone, a mixture of povidone and polyvinyl acetate, hydrogenated vegetable oil, polyethylene glycol, glyceryl behenate and glyceryl palmitostearate and a lubricant optionally in combination with a filling material and/or other excipients. The said publication does not disclose the use of methacrylate polymers such as Eudragits® to prepare the matrix compositions. Specifically disclosed are sustained release film coated tablet formulation wherein the film coating comprises polymethacrylate such as Eudragit which are hydrophobic and water insoluble in nature.

Although several prior art literature is available on controlled release delivery systems particularly for water soluble drugs, most of them relate to the use of hydrophilic swellable polymers to make a core comprising the active agent that controls the release of the active or the use of a coating composition particularly comprising polymers that exhibit pH dependent solubility to control the release of the active agent. Most of the prior art compositions do not provide solution to control the initial 'burst release' of the water soluble active agent from the core composition, which is highly essential to provide a gradual release of the active agent for extended time duration. Hence, such systems fail to provide desired gradual controlled release profiles of water soluble drugs over extended periods of time. No prior art could be found which describes a controlled release composition comprising a water soluble drug wherein the desired controlled drug release is governed by not only the core matrix composition but also by a hydrophilic pH independent coating composition. Hence, there still exists a need for developing controlled release system for delivery of drugs which releases the drug *in vivo* in a specific manner independent of the pH of the gastric environment. The novel compositions of the present invention overcome the limitations of the prior art.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide novel controlled release pharmaceutical composition comprising a core wherein the core comprises at least one water soluble active agent(s) or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more

pharmaceutically acceptable excipients; and at least one coat; wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time.

It is an objective of the present invention to provide novel controlled release pharmaceutical composition comprising a core and a coat, wherein the core comprises at least one water soluble active agent(s) or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more pharmaceutically acceptable excipients; and wherein the coat comprises at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients; and wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time.

It is also an objective of the present invention to provide novel controlled release pharmaceutical compositions comprising a core and a coat, wherein the core is formulated as a hydrophobic, non-swellable matrix system which controls the rate of release of active agent(s), and the coat comprising of at least one layer provided on the core is formulated as a hydrophilic pH independent system which primarily prevents the initial burst release of the active agent(s); the said composition thus providing therapeutic concentrations of active agent(s) for extended periods of time.

It is an objective of the present invention to provide novel controlled release pharmaceutical composition comprising a core, wherein the core comprises alfuzosin or pramipexole or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof as the active agent; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more pharmaceutically acceptable excipients; and wherein the coat comprises at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients; and wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time.

It is another objective of the present invention to provide process for preparation of such composition.

It is a further objective of the present invention to provide a process for preparation of such composition, which comprises of the following steps:

i. Sifting the active agent(s), lipid component(s), water insoluble release modifier(s) and channel forming agent(s) through a suitable sieve followed by mixing,

ii. Mixing the material of step (i) optionally with one or more pharmaceutically acceptable excipient(s),

iii. Formulating the mixture into a suitable core composition,

iv. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

v. Optionally formulating the coated composition into a suitable dosage form.

It is yet another objective of the present invention to provide method of using such compositions which comprises administering to a subject in need thereof an effective amount of the composition.

The novel controlled release dosage form of the present invention may be preferably in the form of coated tablets or mini-tablets, layered tablets, monolithic tablets, capsules, pellets, granules and other dosage forms particularly suitable for oral administration and may be preferably administered twice daily or once daily.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes novel controlled release pharmaceutical composition comprising a core wherein the core comprises at least one water soluble active agent(s) or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more pharmaceutically acceptable excipients; and at least one coat; wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time. In an embodiment of the present invention, the coat comprises at least one hydrophilic pH independent

polymer(s), optionally with one or more pharmaceutically acceptable excipients.

In a preferred embodiment, the novel controlled release pharmaceutical compositions of the present invention comprises a core and a coat, wherein the core is formulated as a hydrophobic, non-swellable matrix system which controls the rate of release of active agent(s) and the coat comprising of at least one layer provided on the core is formulated as a hydrophilic pH independent system which primarily prevents the initial burst release of the active agent(s); the said composition thus providing therapeutic concentrations of active agent(s) for extended periods of time. In an embodiment, the core composition is preferably formulated as a substantially non-erodible matrix system from which the release of the active agent takes place primarily by diffusion. The coating composition is preferably formulated such that it gets hydrated when exposed to the gastro-intestinal environment and forms a gel-like layer which prevents the initial burst release of the active agent(s) and then also controls the release of the active agent(s) for the initial period. The degree and rate of hydration of the hydrophilic pH independent polymer(s) in the coat governs the initial release pattern of the active agent(s). In an embodiment, the coating layer preferably erodes gradually after about 2-8 hours of administration to a subject thus exposing the core matrix composition from which the active agent(s) diffuses out into the gastro-intestinal tract in the desired controlled manner for an extended time period.

In an embodiment, the hydrophobicity of the core is primarily due to the presence of a substantially high concentration of the lipophilic components and/or the water insoluble release modifier(s). Preferably the core composition of the present invention has been devised in such a manner that the release of the active agent(s) from the core matrix takes place predominantly by diffusion particularly through the channels in the coat comprising at least one hydrophilic pH independent polymer which allows the slow introduction of aqueous fluids into the core, thereby controlling the rate of initial drug release from the core gradually in the desired manner for an extended period of time into the desired environment irrespective of the pH of the environment.

In another embodiment, the composition of the present invention behaves as a gastro-retentive system wherein the gastro-retentivity is achieved by mucoadhesion, floatation and/or increasing the residence time of the composition in the gastro-intestinal tract

particularly the stomach. The coating composition preferably provides mucoadhesivity to the compositions of the present invention. Further, the core composition of the present invention might be formulated in such a manner which leads to floatation of the dosage form in the contents of the gastro-intestinal tract for an extended duration by suitably selecting the nature and quantities of the excipients used to formulate the composition. In a further embodiment, the increase in the residence time of the composition in the gastro-intestinal tract particularly the stomach is achieved by incorporating a fatty component such as a triglyceride in the composition or administering the composition with food. However, the formulation of the composition of the present invention as a gastro-retentive system by one or more methods depends on the nature, site of absorption and desired activity of the active agent(s) present in the composition. This particular phenomenon of gastro-retention may help in the increased rate and extent of absorption of active agent(s) from the gastrointestinal tract. For example, alfuzosin is reported to be absorbed more in the proximal upper parts of the tract (duodenum and jejunum) and hence such a phenomenon might contribute to enhancement of absorption and improved bioavailability of the said active agent.

In a preferred embodiment of the present invention, the water soluble active agent(s) used are particularly those which possess acceptable aqueous solubility selected from but not limited to a group comprising alfuzosin, pramipexole, lamotrigine, bumetanide, niacin, metformin, diltiazem, buspirone, tramadol, gabapentin, verapamil, metoprolol, carbidopa, levodopa, carbamazepine, morphine, pseudoephedrine, cisapride, pilocarpine, methylphenidate, nifedipine, nicardipine, felodipine, captopril, terfenadine, pentoxifylline, fenofibrate, acyclovir, zidovudine, moclobemide, potassium chloride, citalopram, cladribine, loratadine, pancrelipase, lithium carbonate, orphenadrine, ketoprofen, procainamide, ferrous sulfate, nefazodone, lovastatin, simvastatin, pravachol, hydromorphone, ticlopidine, selegiline, alprazolam, divalproex, phenytoin, nitroglycerine, isosorbide, and the like or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. In a preferred embodiment of the present invention, the water soluble active agent is alfuzosin or pramipexole or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. Other active agents that can be used in the compositions of the present

invention include but not limited to antihyperglycemics such as sulfonylureas e.g. glibenclamide, glipizide, gliclazide; thiazolidinediones e.g. rosiglitazone, pioglitazone; prokinetics; antihypertensives; lipid lowering agents; antihistamines; antiemetics; analgesics; anti-inflammatory agents; tranquilizers; sedatives; hypnotics; antibiotics; antifungals; steroids; and the like or mixtures thereof. In an embodiment of the present invention, the water soluble active agents are preferably low dose drugs such as those having a human dose of about 0.1 mg to about 100 mg per day.

In an embodiment, the present invention provides novel controlled release pharmaceutical composition comprising a core wherein the core comprises alfuzosin or pramipexole or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more pharmaceutically acceptable excipients; and a coat wherein the coat comprises at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients; and wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time.

The lipid system used to formulate the core composition of the present invention comprises at least one lipid component which is preferably a waxy material and aids in providing a controlled release of the active agent. The lipid system of the present invention comprises one or more excipients that are particularly lipophilic in nature. The components of the lipid system primarily help in providing a lipid based matrix system comprising the active agent. Examples of lipid component used in the present invention include but not limited to glyceryl behenate such as Compritol® ATO888, Compritol® HD ATO5, and the like; hydrogenated vegetable oil such as hydrogenated castor oil e.g. Lubritab® and the like; and glyceryl palmitostearate such as Precirol® ATO5 and the like; waxes such as carnuba wax, beeswax, and the like; fatty substances such as one or more triglycerides; or mixtures thereof. The lipid component is preferably a non-digestible lipid constituting about 5-90% by weight of the total composition and helps in releasing active agent for a desired time period particularly with a pH independent release profile.

In an embodiment, the water insoluble release modifier used in the core composition of the present invention is selected from but not limited to a group comprising methacrylic acid copolymers such as Eudragit® L100/S100/L100-55 and the like; aminoalkyl methacrylate copolymers such as Eudragit® E100/EPO and the like; ammonioalkyl methacrylate copolymers such as Eudragit® RL100/RL30D/RLPO, Eudragit® RS100/RS30D/RSPO and Eudragit® RD100 and the like or mixtures thereof. The use of methacrylic acid copolymers either alone or in specific combinations is governed by the nature of the active agent(s) intended to be used in the compositions of the present invention.

The channel forming agent used in the present invention is selected from but not limited to a group comprising lactose, maltodextrin, fructose, sucrose, mannitol, sorbitol and xylitol; polyethylene glycol such as PEG 100, PEG 400, PEG 2000, PEG 6000 and PEG 10,000; polyvinylpyrrolidone; sodium chloride; sodium citrate; citric acid; water soluble celluloses such as low viscosity hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose and the like or mixtures thereof.

In another embodiment, the coating composition is useful for sustaining the release of the active agent(s) from the core. The coating composition comprises of at least one hydrophilic pH independent polymer(s). The hydrophilic pH independent polymer(s) is selected from but not limited to a group comprising cellulose ethers such as methylcellulose, hydroxyethylcellulose, propylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, carboxymethylcellulose or its sodium salt, and the like or mixtures thereof. Preferably the hydrophilic pH independent polymer is a non-ionic polymer, more preferably a cellulosic polymer. In a preferred embodiment, the hydrophilic pH independent polymer used is hydroxypropyl methylcellulose. Preferably the hydrophilic pH independent polymer constitutes about 1% to about 99% w/w of the total solid content in the coating composition. In an embodiment, the coating composition may optionally contain other pharmaceutically acceptable excipients selected from but not limited to a group comprising lubricants, plasticizers and colorants and the like known to the art used either alone or in combination thereof.

In an embodiment of the coating composition of the present invention, the hydrophilic pH independent polymer is a low viscosity grade polymer or a high viscosity grade polymer, preferably a high viscosity grade polymer. Upon contact with an aqueous

environment, the said polymer gets hydrated and controls the initial release of the active agent(s). The site, rate and duration of the release of the active agent(s) is controlled by varying specific parameters such as the thickness of the coating and the amount of hydrophilic pH independent polymer(s) used to formulate the coating composition. The use of more viscous polymer(s) in the coating composition also aids in increasing the residence time of the composition in the gastro-intestinal tract. Particularly hydroxypropyl methylcellulose is used as the hydrophilic pH independent polymer(s) in the coating composition. A low viscosity hydroxypropyl methylcellulose is defined as one having preferably a molecular weight of 55,000 or greater and viscosity of 800 mPas or less. A high viscosity hydroxypropyl methylcellulose is defined as one having preferably a molecular weight of 60,000 or greater and viscosity of 1000 mPas or greater. A mixture of low viscosity and high viscosity hydroxypropyl methylcellulose polymers may also be used to formulate the coating composition of the present invention.

In an embodiment of the present invention, the active agent(s) is released mainly by diffusion mechanism from the composition comprising a core and at least one coat. The hydrophilic pH independent polymer preferably the high viscosity (high molecular weight) HPMC in the coat of the composition upon contact with the aqueous fluids gets wet and the HPMC begins to hydrate, forming a gel-like layer. Over a period of time the aqueous fluid permeates into the coat further and increases the thickness of the gel-like layer. Further hydration of the coat will lead to fully hydrated coat layer and at the same time core is also simultaneously hydrated. This phenomenon provides barrier to the initial burst release of the active agent(s) from the core tablet. The drug being water soluble in nature shall diffuse through the gel-like layer initially. Any further hydration to the fully hydrated gel layer leads to dissolution of the loose gel-like layer into the aqueous fluids and hence, during this period drug release from the coated layer may be by both diffusion and erosion. It was observed that the hydrated gel-like layer almost completely eroded in less than about 6 hours in the *in vitro* dissolution media (0.01N HCl or pH 6.8 phosphate buffer) irrespective of dissolution method. The aqueous fluids continue to permeate towards the inner core composition to achieve sustained release of the active agent(s) by diffusion mechanism. The core matrix composition comprising a lipid component such as glyceryl behenate along with an optimum combination of water insoluble release modifier(s) such as Eudragit® RSPO and Eudragit® RLPO and

a channel former(s) provides sustained release of active agent(s). Presence of a combination of water insoluble release modifier(s) and channel former(s) provides desired intactness to the lipid matrix composition and thereby aids in both initial as well as later stages of the drug release from the lipid matrix system by diffusion mechanism to achieve completeness of release of active agent(s).

In a further embodiment, the plasticizer(s) used in the coating composition in the present invention is selected from but not limited to a group comprising acetyl citrate, triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, dibutyl phthalate, dioctyl phthalate, dibutylsebacate, triethyl citrate, tributylcitrate, glyceryltributyrate, glyceryl triacetate, polyethylene glycol, propylene glycol, and the like or mixtures thereof. In a preferred embodiment, the plasticizer(s) used is polyethylene glycol. Preferably the plasticizer(s) constitutes about 0.1-80% w/w, more preferably about 1-55% w/w of the hydrophilic pH independent polymer content of the coating composition. In an embodiment, the polyethylene glycol useful as a plasticizer is selected from but not limited to a group comprising PEG 100, PEG 400, PEG 2000, PEG 6000 and PEG 10,000. Optionally lubricants useful in the coating composition may be selected from but not limited to the group comprising talc, colloidal silica and magnesium stearate, and the like or mixtures thereof. In a preferred embodiment of the present invention, the coat constitutes about 0.5% to about 25% by weight more preferably from about 2% to about 15% by weight of the controlled release composition.

The pharmaceutically acceptable excipients that can be used for preparation of such compositions are selected from but not limited to diluents, disintegrants, binders, fillers, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, organic solvents, stabilizers, preservatives, lubricants, glidants, chelating agents, surfactants, and the like known to the art used either alone or in combination thereof. In an embodiment, the filler(s) used in the present invention is selected from but not limited to a group comprising lactose, mannitol, sorbitol, starch, microcrystalline cellulose, xylitol, fructose, sucrose, dextrose, dicalcium phosphate, calcium sulphate and the like or mixtures thereof. The disintegrants used in the present invention include but not limited to starch or its

derivatives, partially pregelatinized maize starch, croscarmellose sodium, sodium starch glycollate, and the like used either alone or in combination thereof. The lubricants used in the present invention include but not limited to talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil and the like used either alone or in combination thereof.

The controlled release dosage form may be in the form of tablets such as layered or monolithic tablet, mini-tablets such as such as layered or monolithic mini-tablets, capsules, pellets, granules, patches, powders and other dosage forms suitable for oral administration. In a preferred embodiment, the composition of the present invention is in the form of layered or monolithic tablets/mini-tablets. The composition can be prepared by either direct compression, dry compression (slugging) or by granulation. In a preferred embodiment of the present invention, the oral composition is prepared by direct compression or compaction granulation. The composition prepared by granulation technique is either by aqueous or non-aqueous technique or melt granulation technique. The non-aqueous solvent used is selected from a group comprising dehydrated alcohol, isopropyl alcohol, methylene chloride or acetone. In an embodiment, the compositions of the present invention are in the form of granules, beads or pellets that may be further compacted, compressed, or molded, or made into capsules. The compositions may be coated with a functional coating. By the term 'functional coating' it is herein implied that the coating composition comprises a part of the active agent(s) and/or the composition comprises excipients which aid in controlling the rate of release of the active agent(s) and/or the composition comprises additionally another active agent which is different from the active agent present in the core composition. The composition may be formulated as layered tablets comprising at least two layers wherein the same active agent is present in all the layers exhibiting different release profiles or one or more additional active agent(s) is present in the layers exhibiting different release profiles. The coating composition employed in the present invention may be an aqueous, non-aqueous or a hydro-alcoholic system. The solvents used to prepare a non-aqueous coating composition is selected from but not limited to a group comprising dehydrated alcohol, isopropyl alcohol, methylene chloride, acetone or any other solvent known to the art for such use, or mixtures thereof.

In an embodiment, the controlled release core compositions of the present invention comprises of at least two fractions wherein one fraction comprises the active agent(s), the lipid system, water insoluble release modifier(s) and the channel forming agent(s) optionally one or more pharmaceutically acceptable excipients in such quantities so as to provide an immediate release of the active agent(s) from the core matrix and the other fraction comprises the active agent(s), the lipid system, water insoluble release modifier(s) and the channel forming agent(s) optionally one or more pharmaceutically acceptable excipients in such quantities so as to provide a sustained release of the active agent(s) from the core matrix. Preferably, the lipid system and the water insoluble release modifier(s) are present in low quantities in one fraction thus providing immediate release of the active agent(s) from the core matrix as compared to the lipid system and the water insoluble release modifier(s) present in other fraction thus providing sustained release of the active agent(s) from the core matrix.

In a preferred embodiment of the present invention, the core of the composition comprises active agent(s) from about 0.1% w/w to about 98.9% w/w, a lipid system comprising at least one lipid component(s) from about 0.5% w/w to about 85% w/w, at least one water insoluble release modifier(s) from about 0.4% w/w to 70% w/w, and at least one channel forming agent(s) from about 0.1% w/w to 80% w/w, optionally one or more pharmaceutically acceptable excipients from about 0.1% w/w to 80% w/w of the core composition.

In an embodiment of the present invention, the active agent(s) is released mainly by diffusion mechanism from the controlled release compositions. A portion of the lipid matrix is embedded within the channel forming agent(s) which slowly but continuously forms channels in the lipid matrix to give a sustained release of the active agent(s). The release modifier(s) modifies the release of the active agent in the initial stages and also extends the release throughout the desired period at preferably a constant and predetermined rate. The combination of the lipid system and the release modifier(s) aids in enhancing and maintaining the intactness of the composition until the entire active agent is released. Preferably the ratio of the lipid system and the release modifier(s) is from about 1:20 to about 20:1. In a preferred embodiment, the composition is in the form of tablet that when tested in vitro retains its original shape in both 0.01N Hydrochloric acid and pH 6.8 phosphate buffer even after 6 hours at

100rpm USP type-2 and also in 100rpm USP type-1 apparatus and releases the active agent in vivo primarily by diffusion mechanism. However, the duration of intactness of composition of present invention both in vitro and in vivo can be altered by varying the concentration of particularly lipid system and release modifier(s). It has been surprisingly found by the inventors of the present invention that irrespective of dissolution method and the media used, the composition releases the desired active agent(s) over an extended time period preferably over a period of 8-24 hours in a controlled fashion, which is necessary to maintain the desired therapeutic plasma levels of the active agent(s). The composition of the present invention is capable of releasing the active agent(s) along the gastrointestinal tract and independent of pH conditions of gastrointestinal tract to achieve and maintain therapeutic concentrations of the active agent(s) for extended time duration.

In another embodiment, the controlled release compositions of the present invention are easy to manufacture and are primarily non-erodible type systems. The active agent(s) is primarily released by diffusion mechanism and independent of the gastro-intestinal pH. The dosage form remains almost intact even after the complete release of the active agent, which leads to a more reliable drug delivery system providing a pH independent, predictable and reproducible release profile of active agent(s), particularly as evidenced by the in vitro dissolution study. In another embodiment, the controlled release compositions of the present invention release the active agent(s) in a consistent and uniform manner and are devoid of substantial variations in the release of the active agent(s) between individual unit dosage forms.

In an embodiment of the present invention, the controlled release oral dosage form composition exists preferably as a coated lipid based single layered matrix tablet. The matrix composition of the present invention comprises the active agent(s) preferably in a range of about 0.5% to about 50% by weight of the composition; the lipid system preferably in a range of about 1% to about 70% by weight of the composition, water insoluble release modifier preferably in a range of about 1% to about 60% by weight of the composition; the channel forming agent preferably in a range of about 1% to about 70% by weight of the composition; and lubricants/glidants from about 0.5% to about 5% by weight of the composition.

In another embodiment of the present invention; the novel controlled release pharmaceutical composition comprises metformin in the core additionally with at least one another antihyperglycemic active agent such as glibenclamide, rosiglitazone, or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof wherein the said another active agent is present either in the core or in the coat or in both; a lipid system comprising at least one lipid component; at least one water insoluble release modifier; at least one channel forming agent; and optionally, one or more pharmaceutically acceptable excipients. In a further embodiment, the pharmaceutical composition is formulated as a layered tablet comprising the same or different antihyperglycemic active agent in the layers or may be formulated as coated tablet with a functional coating wherein at least one of the antihyperglycemic active agent(s) is present in the coat. The at least one another antihyperglycemic active agent may be present in an immediate release form or a controlled release form.

In another embodiment, the core composition of the present invention additionally comprise at least one another release modifier selected from but not limited to a group comprising cellulosic polymer, gum, hydrophilic polysaccharides such as alginates, chitosan, scleroglucan or semi-synthetic polysaccharides and the like or mixtures thereof. The cellulosic polymer(s) of the present invention is selected from but not limited to a group comprising hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and the like or mixtures thereof; alkyl celluloses such as ethyl cellulose, methylcellulose and the like or mixtures thereof; hydroxypropyl methylcellulose; hydroxypropyl ethylcellulose; carboxyalkyl celluloses such as carboxymethyl cellulose, carboxyethyl cellulose and the like or mixtures thereof. The gum used in the present invention is selected from but not limited to a group comprising xanthan gum, guar gum, gum arabic, carrageenan gum, karaya gum, locust bean gum, acacia gum, tragacanth gum, agar and the like or mixtures thereof.

In another embodiment, the present invention also provides process for preparation of such novel compositions. In a further embodiment, the present invention provides a process for preparation of such composition, which comprises of the following steps:

i. Sifting the active agent(s), lipid component(s), water insoluble release modifier(s)

and channel forming agent(s) through a suitable sieve followed by mixing,

ii. Mixing the material of step (i) optionally with one or more pharmaceutically acceptable excipient(s),

iii. Formulating the mixture into a suitable core composition,

iv. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

v. Optionally formulating the coated composition into a suitable dosage form.

In a further embodiment, the present invention provides a process for preparation of such composition, which comprises of the following steps:

i. Sifting the active agent(s), lipid component(s), water insoluble release modifier(s), channel forming agent(s) and lubricant(s) through a suitable sieve,

ii. Separately mixing the active agent(s) and the channel forming agent(s) sifted in step (i),

iii. Separately mixing the lipid component(s) and water insoluble release modifier(s) sifted in step (i),

iv. Mixing the blend of step (ii) with the blend of step (iii),

v. Mixing the blend of step (iv) with a portion of a lubricant(s) to obtain a homogeneous blend,

vi. Slugging the blend of step (v) followed by breaking the slugs and sifting the material through suitable sieve to obtain granules,

vii. Optionally mixing the sifted material of step (vi) with other pharmaceutically acceptable excipient(s),

viii. Adding the remaining portion of lubricant to the material of step (vii) and mixing,

ix. Formulating the mixture into a suitable core composition,

x. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

xi. Optionally formulating the coated composition into a suitable dosage form.

In a still further embodiment, the present invention provides a process for preparation of such composition, which comprises of the following steps:

i. Mixing the active agent(s), water insoluble release modifier(s) and channel forming agent(s),

ii. Melting the lipid system and maintaining the molten mixture at least 10°C above the melting point of the lipid component having the highest melting point,

iii. Dispersing the mixture of step (i) in the molten mixture of step (ii) to obtain a homogeneous dispersion and sifting the same through a sieve,

iv. Optionally mixing the sifted material with a lubricant(s) and/or other pharmaceutically acceptable excipient(s),

v. Formulating the mixture into a suitable core composition,

vi. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

vii. Optionally formulating the coated composition into a suitable dosage form.

In yet another embodiment of the present invention is provided method of using such composition, which comprises administering to a subject in need thereof an effective amount of the composition comprising the active agent(s). For example, the composition comprising alfuzosin as the active agent is useful in the treatment of moderate to severe symptoms of benign prostatic hyperplasia. The composition comprising pramipexole as active agent is useful particularly for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The examples given below serve to illustrate embodiments of the present invention. However they do not intend to limit the scope of the present invention.

EXAMPLES

Example-1:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Alfuzosin hydrochloride	10.0
2.	Glyceryl behenate (Compritol® ATO888)	120.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	30.0

4.	Ammonioalkyl methacrylate copolymer (Eudragit® RLPO)		80.0
5.	Mannitol		81.7
6.	Magnesium stearate		3.3
Coating composition			
7.	Hydroxypropyl methylcellulose		10.83
8.	Polyethylene glycol (PEG 6000)		1.63
9.	Talc		2.85
10.	Titanium dioxide		0.95
11.	Methylene chloride	q.s. (lost in processing)	
12.	Dehydrated alcohol	q.s. (lost in processing)	

Procedure:

i) Alfuzosin hydrochloride and Mannitol were sifted through #40 mesh and mixed together.

ii) Glyceryl behenate, Eudragit® RSPO and Eudragit® RLPO were separately sifted through #40 mesh and then mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Magnesium stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Magnesium stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Methylene chloride and Dehydrated alcohol were stirred together in a container.

viii) Talc and Titanium dioxide were dispersed together in a portion of solvent mixture of step (vii) in a homogenizer.

ix) Polyethylene glycol was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

x) The dispersion of step (viii) was added to the mixture in step (ix) followed by mixing.

xi) The tablets of step (vi) were finally coated with the coating dispersion of step (x).

Example-2:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Alfuzosin hydrochloride	10.0
2.	Glyceryl behenate (Compritol® ATO888)	100.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	21.0
4.	Ammonioalkyl methacrylate copolymer (Eudragit® RLPO)	9.0
5.	Lactose	17.0
6.	Magnesium stearate	3.0
Coating composition		
7.	Hydroxypropyl methylcellulose	5.42
8.	Triacetin	1.63
9.	Talc	2.85
10.	Titanium dioxide	0.95
11.	Methylene chloride	q.s. (lost in processing)
12.	Dehydrated alcohol	q.s. (lost in processing)

Procedure:

i) Alfuzosin hydrochloride was sifted through #40 mesh followed by blending with #40 mesh passed Lactose, Eudragit® RSPO and Eudragit® RLPO.

ii) The blend was dispersed uniformly in molten Compritol® ATO888 and allowed to cool.

iii) The uniformly dispersed blend was passed through #30 mesh to obtain granules.

iv) Magnesium stearate was sifted through #60 mesh followed by blending with the granules of step (iii).

v) The granules of step (iv) were compressed to obtain tablets.

vi) Methylene chloride and Dehydrated alcohol were stirred together in a container.

vii) Talc and Titanium dioxide were dispersed together in a portion of solvent mixture of step (vi) in a homogenizer.

viii) Triacetin was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

ix) The dispersion of step (vii) was added to the mixture in step (viii) followed by mixing.

x) The tablets of step (v) were finally coated with the coating dispersion of step (ix).

Example-3:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Metformin hydrochloride (Micronized)	500.0
2.	Glyceryl behenate (Compritol® ATO888)	180.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	40.0
4.	Xanthan gum	60.0
5.	Sorbitol	50.0
6.	Calcium stearate	10.0
Coating composition		
7.	Hydroxyethyl cellulose	21.66
8.	Triacetin	3.26
9.	Silicon dioxide	5.70
10.	Titanium dioxide	1.90
11.	Methylene chloride	q.s. (lost in processing)
12.	Dehydrated alcohol	q.s. (lost in processing)

Procedure:

i) Metformin hydrochloride and Sorbitol were sifted through #40 mesh and mixed together.

ii) Glyceryl behenate, Ammonioalkyl methacrylate copolymer and Xanthan gum were separately sifted through #40 mesh and then mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Calcium stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Calcium stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Methylene chloride and Dehydrated alcohol were stirred together in a container.

viii) Silicon dioxide and Titanium dioxide were dispersed together in a portion of solvent mixture of step (vii) in a homogenizer.

ix) Triacetin was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxyethyl cellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

x) The dispersion of step (viii) was added to the mixture in step (ix) followed by mixing.

xi) The tablets of step (vi) were finally coated with the coating dispersion of step (x).

Example-4:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Methylphenidate hydrochloride (Micronized)	54.0
2.	Glyceryl palmitostearate	140.0
3.	Aminoalkyl methacrylate copolymer	65.0
4.	Ammonioalkyl methacrylate copolymer	23.0
5.	Lactose	40.0
6.	Zinc stearate	3.0
Coating composition		
7.	Hydroxypropyl methylcellulose	5.0
8.	Triethyl citrate	0.8
9.	Talc	0.8
10.	Titanium dioxide	0.9
11.	Purified water	q.s. (lost in processing)

Procedure:

i) Methylphenidate hydrochloride and Lactose were sifted through #40 mesh and mixed together.

ii) Glyceryl palmitostearate, Aminoalkyl methacrylate copolymer and Ammonioalkyl methacrylate copolymer were separately sifted through #40 mesh and then mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Zinc stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Zinc stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Talc and Titanium dioxide were dispersed together in a portion of Purified water in a homogenizer.

viii) Triethyl citrate was dissolved in remaining portion of Purified water mixture with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

ix) The tablets of step (vi) were finally coated with the coating dispersion of step (viii).

Example-5:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Niacin	500.0
2.	Hydrogenated castor oil	173.0
3.	Methacrylic acid copolymer	52.0
4.	Ammonioalkyl methacrylate copolymer	116.0
5.	Dextrose	50.0
6.	Magnesium stearate	9.0
Coating composition		
7.	Hydroxypropyl methylcellulose	20.0
8.	Polyethylene glycol	2.5
9.	Talc	4.5
10.	Titanium dioxide	2.0
11.	Methylene chloride	q.s. (lost in processing)
12.	Isopropyl alcohol	q.s. (lost in processing)

Procedure:

i) Niacin and Dextrose were sifted through #40 mesh and mixed together.

ii) Hydrogenated castor oil, Methacrylic acid copolymer and Ammonioalkyl methacrylate copolymer were separately sifted through #40 mesh and then

mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Magnesium stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Magnesium stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Methylene chloride and Isopropyl alcohol were stirred together in a container.

viii) Talc and Titanium dioxide were dispersed together in a portion of solvent mixture of step (vii) in a homogenizer.

ix) Polyethylene glycol was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

x) The dispersion of step (viii) was added to the mixture in step (ix) followed by mixing.

xi) The tablets of step (vi) were finally coated with the coating dispersion of step (x).

Example-6:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Pramipexole dihydrochloride monohydrate	4.5
2.	Glyceryl behenate	105.0
3.	Aminoalkyl methacrylate copolymer	105.0
4.	Fructose	76.5
5.	Calcium stearate	9.0
Coating composition		
6.	Hydroxypropyl cellulose	10.8
7.	Triacetin	1.6
8.	Silicon dioxide	2.8
9.	Titanium dioxide	0.9
10.	Methylene chloride	q.s. (lost in processing)

11. Dehydrated alcohol q.s. (lost in processing)

Procedure:

i) Pramipexole dihydrochloride monohydrate and Fructose were sifted through #40 mesh and mixed together.

ii) Glyceryl behenate and Aminoalkyl methacrylate copolymer were separately sifted through #40 mesh and then mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Calcium stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Calcium stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Methylene chloride and Dehydrated alcohol were stirred together in a container.

viii) Silicon dioxide and Titanium dioxide were dispersed together in a portion of solvent mixture of step (vii) in a homogenizer.

ix) Triacetin was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxypropyl cellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

x) The dispersion of step (viii) was added to the mixture in step (ix) followed by mixing.

xi) The tablets of step (vi) were finally coated with the coating dispersion of step (x).

Example-7:

S. No.	Ingredient	mg/tablet
Core composition		
1.	Lamotrigine	50.00
2.	Glyceryl behenate	120.00
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	30.00
4.	Ammonioalkyl methacrylate copolymer (Eudragit® RLPO)	80.00
5.	Mannitol	81.75

6.	Magnesium stearate		3.25
Coating composition			
7.	Hydroxypropyl methylcellulose		5.8
8.	Polyethylene glycol (PEG 10,000)		2.6
9.	Talc		2.8
10.	Titanium dioxide		0.9
11.	Methylene chloride		q.s. (lost in processing)
12.	Dehydrated alcohol		q.s. (lost in processing)

Procedure:

i) Lamotrigene and Mannitol were sifted through #40 mesh and mixed together.

ii) Glyceryl behenate, Eudragit® RSPO and Eudragit® RLPO were separately sifted through #40 mesh and then mixed together. The material of step (i) was mixed with the material of step (ii).

iii) A portion of #60 mesh sifted Magnesium stearate was added to blend of step (ii) and mixed.

iv) The material of step (iii) was slugged to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #30 mesh to obtain granules.

v) The remaining portion of #60 mesh sifted Magnesium stearate was added to the granules of step (iv) followed by mixing.

vi) The granules of step (v) were compressed to obtain tablets.

vii) Methylene chloride and Dehydrated alcohol were stirred together in a container.

viii) Talc and Thanium dioxide were dispersed together in a portion of solvent mixture of step (vii) in a homogenizer.

ix) Polyethylene glycol was dissolved in remaining portion of solvent mixture of step (vii) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

x) The dispersion of step (viii) was added to the mixture in step (ix) followed by mixing.

xi) The tablets of step (vi) were finally coated with the coating dispersion of step (x).

Example-8:

S. No.	Ingredient	mg/tablet
	A) Core composition	
1.	Metformin hydrochloride	500.0
2.	Glyceryl behenate (Compritol® ATO888)	550.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	90.0
4.	Lactose	50.0
5.	Hydrogenated castor oil (Lubritab®)	10.0

Procedure:

i) Metformin hydrochloride was sifted through #40 mesh and was blended with Lactose and Ammonioalkyl methacrylate copolymer was passed through #40 mesh.

ii) The blend was dispersed uniformly in molten Glyceryl behenate and allowed to cool down.

iii) The material of step (ii) was passed through #30 mesh.

iv) Hydrogenated castor oil was sifted through #40 mesh and was blended with the material of step (iii).

S. No.	Ingredient	mg/tablet
	B) Core composition	
1.	Glibenclamide	5.0
2.	Glyceryl palmitostearate	22.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RLPO)	20.0
4.	Mannitol	100.0
5.	Croscarmellose sodium	20.0
6.	Magnesium stearate	3.0

Procedure:

i) Glibenclamide, Mannitol and Croscarmellose sodium were sifted together through #40 mesh followed by mixing.

ii) Glyceryl palmitostearate and Ammonioalkyl methacrylate copolymer were mixed together.

iii) The material of step (ii) was added to the material of step (i) followed by mixing. A portion of #60 mesh sifted Magnesium stearate was added and mixed.

iv) The blend of step (iii) was slugged, crushed and passed through #30 mesh to

obtain the granules.

v) Magnesium stearate was sifted through #60 mesh and added to material of step (iv) and mixed.

C) Preparation of tablet

i) The material of step (A) (iv) and step (B) (v) was mixed and compressed into tablet.

D) Coating composition

S. No.	Ingredient	mg/tablet
1.	Hydroxypropyl methylcellulose	15.6
2.	Polyethylene glycol	1.6
3.	Talc	3.6
4.	Titanium dioxide	0.9
5.	Methylene chloride	q.s. (lost in processing)
6.	Dehydrated alcohol	q.s. (lost in processing)

Procedure:

i) Methylene chloride and Dehydrated alcohol were stirred together in a container.

ii) Talc and Titanium dioxide were dispersed together in a portion of solvent mixture of step (i) in a homogenizer.

iii) Polyethylene glycol was dissolved in remaining portion of solvent mixture of step (i) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

iv) The dispersion of step (ii) was added to the mixture in step (iii) followed by mixing.

v) The tablets of step (C) (i) were finally coated with the coating dispersion of step (D) (iv).

Example-9:

A) Core composition

S. No.	Ingredient	mg/tablet
1.	Metformin hydrochloride	500.0
2.	Glyceryl behenate (Compritol® ATO888)	550.0
3.	Ammonioalkyl methacrylate copolymer (Eudragit® RSPO)	90.0
4.	Lactose	50.0
5.	Hydrogenated castor oil (Lubritab®)	10.0

Procedure:

i) Metformin hydrochloride was sifted through #40 mesh and was blended with #40 mesh passed Lactose and Ammonioalkyl methacrylate copolymer.

ii) The blend of step (i) was dispersed uniformly in molten Glyceryl behenate and allowed to cool.

iii) The material of step (ii) was passed through #30 mesh.

iv) Hydrogenated castor oil was sifted through #40 mesh and was blended with the material of step (iii).

v) The granules of step (iv) were compressed to obtain tablets.

B) First Coating composition

S. No.	Ingredient	mg/tablet
1.	Hydroxypropyl methylcellulose	10.83
2.	Polyethylene glycol	1.63
3.	Talc	2.85
4.	Titanium dioxide	0.95
5.	Methylene chloride	q.s (lost in processing)
6.	Dehydrated alcohol	q.s (lost in processing)

Procedure:

i) Methylene chloride and Dehydrated alcohol were stirred together in a container.

ii) Talc and Titanium dioxide were dispersed together in a portion of solvent mixture of step (i) in a homogenizer.

iii) Polyethylene glycol was dissolved in remaining portion of solvent mixture of step (i) with continuous stirring. Hydroxypropyl methylcellulose was slowly added to the mixture with continuous stirring until a uniform dispersion was formed.

iv) The dispersion of step (ii) was added to the mixture in step (iii) followed by mixing.

v) The tablets of step (A) (v) were finally coated with the coating dispersion of step (B) (iv).

C) Second Coating composition

S. No.	Ingredient	mg/tablet
1.	Rosiglitazone maleate	5.3
2.	Hydroxypropyl methylcellulose	20.0
3.	Propylene glycol	4.0

4.	Titanium dioxide	2.0
5.	Talc	0.7
6.	Ethanol	q.s (lost in processing)

Procedure:

i) Rosiglitazone maleate was sifted through #40 mesh .

ii) The material of step (i) was dispersed with continuous stirring in Ethanol followed by Hydroxypropyl methylcellulose, Propylene glycol, Titanium dioxide and Talc, stir to obtain a homogeneous dispersion.

iii) Tablets obtained in step (B) (v) were coated with the dispersion prepared in step (C) (ii) (C).

We claim:

1. A novel controlled release pharmaceutical composition comprising a core wherein the core comprises at least one water soluble active agent(s) or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; a lipid system comprising at least one lipid component(s); at least one water insoluble release modifier(s); at least one channel forming agent(s); and optionally, one or more pharmaceutically acceptable excipients; and at least one coat; wherein the composition provides therapeutic concentrations of active agent(s) for extended periods of time.

2. A composition according to claim 1, wherein the coat comprises at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients.

3. A composition according to claim 1, wherein the core is formulated as a hydrophobic, non-swellable matrix system which controls the rate of release of active agent(s) and the coat comprising of at least one layer provided on the core formulated as a hydrophilic pH independent system which prevents the initial burst release of the active agent(s).

4. A composition according to any of the claims 1-3, wherein the water soluble active agent is selected from a group comprising alfuzosin, pramipexole, lamotrigine, niacin, metformin, diltiazem, buspirone, tramadol, gabapentin, verapamil, metoprolol, carbidopa, levodopa, carbamazepine, morphine, pseudoephedrine, cisapride, pilocarpine, methylphenidine, nifedipine, nicardipine, felodipine, captopril, terfenadine, pentoxifylline, fenofibrate, acyclovir, zidovudine, moclobemide, potassium chloride, citalopram, cladribine, loratadine, pancrelipase, lithium carbonate, orphenadrine, ketoprofen, procainamide, ferrous sulfate, nefazodone, pravachol, hydromorphone, ticlopidine, selegiline, alprazolam, divalproex, phenytoin, nitroglycerine, isosorbide, or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.

5. A composition according to any of the claims 1-3, wherein the water soluble active agent is selected from a group comprising antihyperglycemics; thiazolidinediones; prokinetics; antihypertensives; lipid lowering agents;

antihistaminics; antiemetics; analgesics; anti-inflammatory agents; tranquilizers; sedatives; hypnotics; antibiotics; antifungals; steroids or mixtures thereof.

6. A composition according to claim 5, wherein the water soluble active agent is alfuzosin or pramipexole or their pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.

7. A composition according to any of the claims 1-6, wherein the lipid component used in the core is selected from a group comprising glyceryl behenate, hydrogenated vegetable oil, glyceryl palmitostearate, or mixtures thereof.

8. A composition according to claims 1-6, wherein the water insoluble release modifier(s) used in the core is selected from a group comprising methacrylic acid copolymers; aminoalkyl methacrylate copolymers; ammonioalkyl methacrylate copolymers or mixtures thereof.

9. A composition according to claims 1-6, wherein the channel forming agent used in the core is selected from a group comprising lactose, maltodextrin, fructose, sucrose, mannitol, sorbitol, xylitol, polyethylene glycol, polyvinylpyrrolidone, sodium chloride, sodium citrate, citric acid, water soluble celluloses or mixtures thereof.

10. A composition according to claim 9, wherein the water soluble cellulose used in the core is selected from a group comprising low viscosity hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose or mixtures thereof.

11. A composition according to claim 1, wherein the coating composition for coating the core comprises of at least one hydrophilic pH independent polymer(s) selected from a group comprising cellulose ethers or mixtures thereof.

12. A composition according to claim 11, wherein the cellulose ether is selected from a group comprising methylcellulose, hydroxyethylcellulose, propylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, carboxymethylcellulose or its sodium salt, or mixtures thereof.

13. A composition according to claim 1, wherein the coating composition for coating the core comprises other pharmaceutically acceptable excipients

selected from a group comprising lubricants, plasticizers and colorants used either alone or in combination thereof.

14. A composition according to claim 13, wherein the plasticizer is selected from a group comprising acetyl citrate, triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, dibutyl phthalate, dioctyl phthalate, dibutylsebacate, triethyl citrate, tributylcitrate, glyceryltributyrate, glyceryl triacetate, polyethylene glycol, propylene glycol or mixtures thereof.

15. A composition according to claim 1, wherein the pharmaceutically acceptable excipients are selected from a group comprising diluents, disintegrants, binders, fillers, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, organic solvents, stabilizers, preservatives, lubricants, glidants, chelating agents, surfactants, known to the art used either alone or in combination thereof.

16. A composition according to claim 1, wherein the controlled release dosage form may be administered in the form of tablets, mini-tablets, capsules, pellets, granules, patches, powders and other dosage forms suitable for oral administration.

17. A composition according to claim 16, wherein the controlled release dosage form is in the form of layered or monolithic tablet.

18. A composition according to claim 1, wherein the composition additionally comprises at least one another release modifier selected from a group comprising cellulosic polymer, gum, hydrophilic polysaccharides or semi-synthetic polysaccharides or mixtures thereof.

19. A composition according to claim 18, wherein the cellulosic polymer is selected from a group comprising hydroxyalkyl celluloses; alkyl celluloses; hydroxypropyl methylcellulose; hydroxypropyl ethylcellulose; carboxyalkyl celluloses; or mixtures thereof.

20. A composition according to claim 18, wherein the gum is selected from a group comprising xanthan gum, guar gum, gum arabic, carrageenan gum, karaya gum, locust bean gum, acacia gum, tragacanth gum, agar or mixtures thereof.

21. A composition according to claim 18, wherein the hydrophilic polysaccharides is selected from a group comprising alginates, chitosan, scleroglucan or mixtures thereof.

22. A composition according to claim 1, wherein the core composition comprises of at least two fractions wherein one fraction comprises the active agent(s), the lipid system, water insoluble release modifier(s) and the channel forming agent(s) optionally one or more pharmaceutically acceptable excipients in such quantities so as to provide an immediate release of the active agent(s) from the core matrix and the other fraction comprises the active agent(s), the lipid system, water insoluble release modifier(s) and the channel forming agent(s) optionally one or more pharmaceutically acceptable excipients in such quantities so as to provide a sustained release of the active agent(s) from the core matrix.

23. A process for the preparation novel controlled release pharmaceutical composition according to claim 1, which comprises of the following steps:

i. Sifting the active agent(s), lipid component(s), water insoluble release modifier(s) and channel forming agent(s) through a suitable sieve followed by mixing,

ii. Mixing the material of step (i) optionally with one or more pharmaceutically acceptable excipient(s),

iii. Formulating the mixture into a suitable core composition,

iv. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

v. Optionally formulating the coated composition into a suitable dosage form.

24. A process for the preparation novel controlled release pharmaceutical composition according to claim 1, which comprises of the following steps:

i) Sifting the active agent(s), lipid component(s), water insoluble release modifier(s), channel forming agent(s) and lubricant(s) through a suitable sieve,

ii) Separately mixing the active agent(s) and the channel forming agent(s) sifted in step (i),

iii) Separately mixing the lipid component(s) and water insoluble release modifier(s) sifted in step (i),

iv) Mixing the blend of step (ii) with the blend of step (iii),

v) Mixing the blend of step (iv) with a portion of a lubricant(s) to obtain a homogeneous blend,

vi) Slugging the blend of step (v) followed by breaking the slugs and sifting the material through suitable sieve to obtain granules,

vii) Optionally mixing the sifted material of step (vi) with other pharmaceutically acceptable excipient(s),

viii) Adding the remaining portion of lubricant to the material of step (vii) and mixing,

ix) Formulating the mixture into a suitable core composition,

x) Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

xi) Optionally formulating the coated composition into a suitable dosage form.

25. A process for the preparation novel controlled release pharmaceutical composition according to claim 1, which comprises of the following steps:

i. Mixing the active agent(s), water insoluble release modifier(s) and channel forming agent(s),

ii. Melting the lipid system and maintaining the molten mixture at least 10°C above the melting point of the lipid component having the highest melting point.

iii. Dispersing the mixture of step (i) in the molten mixture of step (ii) to obtain a homogeneous dispersion and sifting the same through a sieve,

iv. Optionally mixing the sifted material with a lubricant(s) and/or other pharmaceutically acceptable excipient(s),

v. Formulating the mixture into a suitable core composition.

vi. Coating the core composition with a coating composition comprising at least one hydrophilic pH independent polymer(s), optionally with one or more pharmaceutically acceptable excipients to obtain the coated composition, and

vii. Optionally formulating the coated composition into a suitable dosage form.

26. A method of using the pharmaceutical composition according to claim 1, which comprises administering to a subject in need thereof an effective amount of the composition.

27. A method of using the pharmaceutical composition according to claim 26, for the treatment of moderate to severe symptoms of benign prostatic hyperplasia; treatment of signs and symptoms of idiopathic Parkinson's disease or treatment of diabetes.

28. Use of a composition according to claim 1, for the manufacture of a medicament for the treatment of moderate to severe symptoms of benign prostatic hyperplasia; treatment of signs and symptoms of idiopathic Parkinson's disease or treatment of diabetes.

29. The pharmaceutical composition substantially as herein described and illustrated by the examples.

30. The process for the preparation of a pharmaceutical composition substantially as herein described and illustrated by the examples.